Statistical Review and Evaluation
(Clinical Review)

NDA#: 20-766/Class 1P

FEB 17 1998

Applicant: Hoffmann-La Roche Inc.

Name of Drug: XENICAL (Orlistat) capsules

Indication: Obesity

Documents Reviewed: Vols. 673-694, NDA Resubmission dated November 17, 1997,

After the NDA submission with the finding of 9, 1, 1 breast cancer cases in the 120 mg orlistat, 60 mg orlistat and placebo treatment groups, respectively, Roche undertook a survey of all 1642 women 45 years and older who had participated in the Phase III clinical trials. The resubmission application extended the survey database date to October 10, 1997. Out of the 1642 patients surveyed in the U.S. and Europe, a total of 1454 (89%) questionnaires were received and entered into the database. The survey extended the observation period to around 3.5 years. The all-patients-combined survey status is displayed in Table 1. It shows that the completion rates are comparable among the treatment groups.

Table 1. All Patients Combined Questionnaire Status

Treatment	Completed	Refused	Died	Outstanding	Total
Placebo	509 (88%)	12 (2%)	4 (0.7%)	54 (9%)	579 (35%)
Xenical 30 & 60 mg	280 (89%)	4 (1%)	1 (0.3%)	31 (10%)	316 (19%)
Xenical 120 mg	665 (89%)	14 (2%)	3 (0.4%)	65 (9%)	747 (45%)
Total	1454 (89%)	30 (2%)	8 (0.5%)	150 (9%)	1642

The 120 mg tid dose is the indicated dose for orlistat. The 30 mg dose was studied in only one of the 7 trials (NM14302) with 91 female patients 45 years or older out of the 161 patients randomized to the 30 mg treatment group. In this table the total number of patients in each treatment group is assigned according to the baseline randomized treatment group for year one.

Table 2 is a summary of the breast cancer cases of women 45 years or older at randomization in the Phase III trials; 11 cases occurred during the clinical trial and 3 occurred during the survey period.

Table 2. Summary of Breast Cancer Cases during Trial Period (11) and Survey (3, in bold)

Protocol (Study Length)	Center	Patient ID	Age at Detection	Treatment Dose	Time from Randomization to Detection (Days)	# cases/n Age≥45 (%)
US						
NM14185 (2 years)	12051/1858	[redacted]	52	120/120 mg	665	4/227 (1.8%)
	10156/436		46	120 mg	32	
	10160/924		61	120/60 mg	436	
	10159/0107		**51**	**120/60 mg**	**1520 (813 days after end of 2 yr trial)**	
	10163/0767		**59**	**Placebo**	**292* (112 days with treatment)**	1/86 (1.2%)
NM14302 (1 year)	12894/68		52	120 mg	55	2/93 (2.2%)
	12895/40		57	120 mg	170	
NM14161 (2 years)	12672/617		54	120 mg	709	1/66 (1.5%)
Europe						
BM14149 (2 years)	12671/1007		53	120 mg	191	3/98 (3.1%)
	12622/DO10		55	120 mg	365	
	12816/AO65		58	120 mg	344	
	12818/F006		47	60 mg	36	1/95 (1.1%)
	12820/H023		54	Placebo	443	1/108 (0.9%)
BM14119C (2 years)	**07571/C017**		**54**	**120 mg**	**1462(646 days after end of 2 yr trial)**	**1/153 (0.7%)**

*Patient withdrew at 112 days, diagnosed at 292? days, and discovered during survey

One placebo case [redacted] occurred during the trial but was discovered in the survey period. For the 120 mg orlistat group, the time between the date of diagnosis of last case on-study and the diagnosis of first case detected off-study was 753 days.

In the resubmission, the sponsor performed epidemiologic analyses on the incidence rates in person-years of clinical trial period and also the clinical trial plus survey period.

Of the 7 phase III clinical trials, three were one-year trials, two were two-year trials and two were 2-year "cross-over" trials. Patients can be classified into the following groups:

Table 3. Patient Classification in the Cross-Over Studies

2-year Cross-Over Study	No. of Patient	On Trial Person-Year
NM14185 1. Placebo (2 yrs)	86	117
2. 120mg (2 yrs)	78	120
3. 120mg (yr 1)/60mg (yr 2)	81/60	72/49
4. 120mg (yr1)/Placebo (yr2)	68/50	58/42
BM14119C 1. Placebo (2 yrs)	62	119
2. Placebo (yr1 only)	29	13
3. Placebo(yr1)/120(yr2)	51/51	51/46
4. 120 (2 yrs)	60	117
5. 120 (yr1 only)	25	12
6. 120 (yr1)/Placebo (yr1)	68/68	69/62

Sponsor's On-Trial Analysis [BEST POSSIBLE]

The sponsor allocated person-years according to the first year treatment group except the group placebo(yr1)/120mg(yr2) (#3, BM14119C) where the second year exposure time on 120 mg was assigned to the 120 mg group. But, the number of patients in each treatment group is according to the first-year-randomized treatment. The results of the on-trial person-time analyses are displayed in Table 4.

Table 4. Sponsor's Epidemiologic Analysis during Trial Period

Treatment Group	No. of Pts	Person-Year on Trial	No. of Observed Cases	Relative Risk	95% Confidence Intervals	p-value (2-sided) Drug vs. Pla	
						Fisher	M-H
Placebo	579	713	1	1.00			
Xenical 30 & 60 mg*	316	395	1	1.81	0.02 - 141.87	1.000	0.672
Xenical 120 mg	747	1096	9	5.86	0.81 - 256.76	0.100	0.057
Xenical 30, 60, 120 mg**	1063	1491	10	4.79	0.68 - 207.67	0.170	0.099
Total		2205					

* 2 arms combined (30 mg, & 60 mg)

** 3 arms combined (30 mg, 60 mg, & 120 mg)

[APPEARS THIS WAY ON ORIGINAL]

Reviewer's Analysis

Dr. Bruce Stadel (HFD-510) designated the person-time of the on-trial period into 6 groups ordered by increasing exposure. For the "cross-over" treatment groups, 120 mg(yr1)/placebo(yr2) and 120 mg(yr1)/60 mg(yr2), the second year person-times were assigned to the groups of placebo after 120 mg and 60 mg orlistat after 120 mg, respectively, as displayed in Table 5.

Table 5. Summary of Person-Year Assignment during Trial Period

Treatment Exposure Group	No. of Pts /yr2*	Person-Year on Trial	Incidence x10^3yr (No. of Cases)
Placebo	579	713	1.4 (1)
Placebo (yr2) after 120 mg (yr 1)	/118	104	- (0)
30 mg	91	81	- (0)
60 mg	225	314	3.18 (1)
60 mg (yr2) after 120 mg (yr1)	/60	49	20.4 (1)
120 mg	747/51**	944	8.47 (8)
Total	1642/229	2205	4.99 (11)

* / yr2: No. of patients contributing the person-years in the second year treatment
** /51: 51 patients in the second year of the placebo(yr1)/120(yr2) group

The test of trend of the 6 exposure groups is p=0.046.

In general, with a randomized clinical trial where patients are followed for a constant period of time, the number of cases is presented in relation to the total number of patients and not to the amount of person-year experience. The analysis result based on the total number of patients should be similar to the analysis based on the person-time when the dropout rates are comparable between the treatment groups. The following analyses consider the event rate as number of patients randomized.

As the 120 mg tid is the indicated dose for orlistat, the comparison between 120 mg orlistat and placebo was conducted for the breast cancer cases. An analysis with study as a stratification factor as well as a pooled analysis were performed. Also, a trend analysis of the three groups of placebo, 30mg/60 mg combined and 120 mg was performed. Table 6 displays the results of the Fisher exact test (conservative) and the asymptotic method (Mantel-Haenszel, Chi-Square) for the breast cancer cases during the Phase III trial.

Table 6. Statistical Analysis on the Breast Cancer Cases During Clinical Trial Period

Study	120 mg Orlistat	30/60 mg Orlistat	Placebo	120 mg Orlistat vs. Placebo Test	p-value (2-sided)	Odds Ratio	(95% C.I.)
				Stratified Analysis			
NM14185	3/227	-	0/ 86	Exact	**0.044**	OR: 7.515[a]	(1.003, 335.8)
BM14149	3/ 98	1/ 95	1/108	M-H	**0.027**[b]	OR: 8.304	(0.956, 72.1)[c]
NM14302	2/ 93	0/159	0/ 90				
BM14119C	0/153	-	0/142	Homogeneity of Odds Ratios[*]		p=0.77 Chi-Square	
NM14161	1/ 66	0/ 62	0/ 57			p=1.00 Exact	
NM14336	0/ 73	-	0/ 58				
BM14119B	0/ 37	-	0/ 38				
				Pooled Analysis			
Total	9/747	1/316	1/579	Fisher's Exact	0.05	OR:7.05	(0.97, 309.5) Exact
	(1.2%)	(0.3%)	(0.2%)	Chi-Square	0.03		(0.89, 55.8) M-H
	Trend Test: p=0.025						

One of the 2 placebo cases (Patient ID [redacted] occurring during the trial period was discovered during the survey period. Table 7 accounts for the one placebo case from survey in the clinical trial analysis; 9 cases of 120 mg orlistat and 2 cases of placebo.

Table 7. Analysis on the Breast Cancer Cases during Clinical Trial Period with Survey Update

Study	120 mg Orlistat	30/60 mg Orlistat	Placebo	120 mg Orlistat vs. Placebo Test	p-value (2-sided)	Odds Ratio	(95% C.I.)
				Stratified Analysis			
NM14185	3/227	-	1/ 86	Exact	**0.126**	OR: 3.516[a]	(0.724, 33.5)
BM14149	3/ 98	1/ 95	1/108	M-H	**0.087**[b1]	OR: 3.518	(0.757, 16.4)[c]
NM14302	2/ 93	0/159	0/ 90				
BM14119C	0/153	-	0/142	Homogeneity of Odds Ratios[*]		p=0.62 Chi-Square	
NM14161	1/ 66	0/ 62	0/ 57			p=0.53 Exact	
NM14336	0/ 73	-	0/ 58				
BM14119B	0/ 37	-	0/ 38				
				Pooled Analysis			
Total	9/747	1/316	2/579	Fisher's Exact	**0.13**	OR: 3.52	(0.72, 33.6) Exact
	(1.2%)	(0.3%)	(0.3%)	Chi-Square	**0.09**		(0.76, 16.4) M-H
	Trend Test: p=0.0734						

[a] Conditional maximum likelihood estimate

[b] M-H variance, p=0.055 with RBG (Robins, Breslow, Greenland) variance [b1] M-H variance, p=0.109 with RBG variance

[c] RBG variance

[*] Large p-value indicates the odds ratios are consistent among studies

Table 9 displays the results for all cases (trial and survey).

Table 9. Statistical Analysis on Breast Cancer Cases During Clinical Trial and Survey Period

Study	120 mg Orlistat	30/60 mg Orlistat	Placebo	120 mg Orlistat vs. Placebo Test	p-value (2-sided)	Odds Ratio	(95% C.I.)
				Stratified Analysis			
NM14185	4/227	-	1/ 86	Exact	**0.077**	OR: 4.175[a]	(0.877, 39.66)
BM14149	3/ 98	1/ 95	1/108	M-H	**0.048[b]**	OR: 3.896	(0.869, 17.48)[c]
NM14302	2/ 93	0/159	0/ 90				
BM14119C	1/153	-	0/142	Homogeneity of Odds Ratios p=0.78 Chi-Square			
NM14161	1/ 66	0/ 62	0/ 57			p=0.81 Exact	
NM14336	0/ 73	-	0/ 58				
BM14119B	0/ 37	-	0/ 38				
				Pooled Analysis			
Total	11/747 (1.5%)	1/316 (0.3%)	2/579 (0.3%)	Exact	**p=0.048**	OR: 4.312	(0.935, 40.15)
				Chi-Square	**p=0.039**		(0.952, 19.53)
	Trend Test: p=0.023						

[a] Conditional maximum likelihood estimate
[b] M-H variance, p=0.076 with RBG variance
[c] RBG variance

The stratified analyses were consistent in showing the homogeneity of the odds ratios among the studies. The stratified analyses, the pooled analyses, as well as the reviewer's epidemiologic analysis (trend on 6 on-trial exposure groups) all showed statistically significant differences in number of breast cancer cases between 120 mg orlistat treated and placebo treated patients. In addition, the trend analysis of the placebo, 30/60 mg orlistat, and 120 mg orlistat treatment groups showed statistically significant results.

Lastly, we requested the sponsor to perform a time-to-event analysis on the three groups of placebo, 30/60 mg orlistat, and 120 mg orlistat. The log-rank test on the null hypothesis that all groups have the same survivor function was 0.07 during the trial period.

Reviewer's Conclusions: [redacted]

1. For randomized clinical trials with a constant follow-up period, it is usually sufficient to present the number of cases in relation to the number of patients randomized. For this reason, we performed analyses that looked at event rates.
2. Analyses stratifying by study suggest that the event rate is consistent across studies.
3. For safety evaluation, the p-value may not need to meet the standard $p \leq 0.05$ (2-sided) level of significance as for an efficacy evaluation.
4. There are at least strong trends indicating an increase in breast cancer cases for 120 mg compared to placebo.

[redacted]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius [redacted] 2-17-98

cc:
Arch NDA 20-766
HFD-510
HFD-510/EColman, BStadel, GTroendle, SSobel, MHess
HFD-715/LPian, Division 2 file
HFD-720/YTsong
Chron.

[redacted]

Hess

FEB 11 1998

ORLISTAT AND BREAST CANCER

1. BACKGROUND

1.1 BREAST CANCER

BREAST CANCER IS VERY RARE IN MEN AND IN WOMEN LESS THAN 20 YEARS OF AGE. FOR U.S. WOMEN WHO WERE 20 YEARS OF AGE OR OLDER WHEN RECEIVING A BREAST CANCER DIAGNOSIS IN 1997, THE RATE OF DIAGNOSIS FOR THE AGE GROUPS 20-44 YEARS AND 45 YEARS OR OLDER WERE APPROXIMATELY:

AGE GROUP 20-44: 25,500 CASES* IN 37,544,000 WOMEN,** OR ABOUT ONE CASE IN EVERY 1472 WOMEN

AGE GROUP ≥45: 154,700 CASES* IN 49,020,000 WOMEN,** OR ABOUT ONE CASE IN EVERY 319 WOMEN

*AMERICAN CANCER SOCIETY:
http://www.cancer.org/statistics/97bcff/who.html
**U.S. CENSUS BUREAU:
http://www.census.gov/population/www/estimates/nation2.html

2.2 ANTI-OBESITY DRUG USE

IN THE U.S. DURING 1997:

ABOUT [redacted] MILLION PRESCRIPTIONS FOR ANTI-OBESITY DRUGS WERE DISPENSED (estimated total for chain, independent, food store, and mail order pharmacies*), and

THE APPROXIMATE DISTRIBUTION OF ANTI-OBESITY DRUG PRESCRIBING BY SEX AND AGE WAS:

UNSPECIFIED
MEN, ALL AGES
WOMEN 20-44 YEARS OF AGE
WOMEN ≥45 YEARS OF AGE

[redacted]

(estimated from records of visits to office-based physician practices in the U.S.**)

[redacted]

Cc: NDA 20-766

2/11/98
ok
for distribution

[redacted]

3. ORLISTAT AND BREAST CANCER IN THE PHASE 3 CLINICAL TRIALS

3.1 DESCRIPTION OF THE CLINICAL TRIALS

THE PHASE 3 CLINICAL TRIALS OF ORLISTAT BEGAN IN 1992 AND ENDED IN 1996. THERE WERE SEVEN TRIALS IN TOTAL: FOUR IN THE U.S., TWO IN EUROPE, AND ONE IN THE U.K. APPROXIMATELY 80% OF THE PATIENTS STUDIED WERE CAUCASIAN WOMEN.

THE SEVEN PHASE 3 CLINICAL TRIALS WERE ALL RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDIES, WHICH HAD LEAD-IN PERIODS DURING WHICH THE PATIENTS WERE TREATED WITH DIET AND PLACEBO. AT THE END OF THE LEAD-IN PERIODS, PATIENTS WERE RANDOMIZED TO TREATMENT WITH ORLISTAT OR PLACEBO. RANDOMIZATION WAS CARRIED OUT IN TWO STRATA, WHICH WERE DEFINED BY THE AMOUNT OF WEIGHT LOST DURING THE LEAD-IN PERIODS ($\leq$2 kg versus >2 kg for the six studies with 4-5 week lead-in periods, and $\leq$10% versus >10% of initial weight for the one study with a 6-month lead-in period).

THERE WERE THREE 1-YEAR TRIALS, TWO 2-YEAR TRIALS, AND TWO 2-YEAR CROSSOVER TRIALS WITH REASSIGNMENT OF STUDY DRUG AT THE END OF THE FIRST YEAR. A TOTAL OF 4188 PATIENTS WERE RANDOMIZED. OF THESE 4188 PATIENTS:

794 (19%) WERE MEN
1752 (42%) WERE WOMEN <45 YEARS OF AGE AT RANDOMIZATION
1642 (39%) WERE WOMEN $\geq$45 YEARS OF AGE AT RANDOMIZATION

3.2 BREAST CANCER DIAGNOSED "ON-STUDY" DURING THE CLINICAL TRIALS

DURING THE SEVEN CLINICAL TRIALS, BREAST CANCER WAS NOT DIAGNOSED IN ANY MEN OR ANY WOMEN <45 YEARS OF AGE AT RANDOMIZATION.

ELEVEN WHITE WOMEN $\geq$45 YEARS OF AGE AT RANDOMIZATION RECEIVED DIAGNOSES OF BREAST CANCER WHILE THEY WERE "ON-STUDY" IN THE TRIALS. THE MEDIAN AGE AT DIAGNOSIS WAS 53 YEARS AND THE RANGE WAS 46-61 YEARS. FOUR OF THE ELEVEN CAME FROM THE RANDOMIZATION STRATUM THAT LOST $\leq$2 KG OR $\leq$10% OF INITIAL WEIGHT DURING THE LEAD-IN PERIODS, AND SEVEN FROM THE STRATUM THAT LOST >2 KG OR >10% OF INITIAL WEIGHT. THE DISTRIBUTION BY TREATMENT GROUP AT THE BEGINNING OF THE TRIALS WAS:

9 CASES/747 WOMEN RANDOMIZED TO ORLISTAT 120 MG TID
1 CASE /225 WOMEN RANDOMIZED TO ORLISTAT 60 MG TID
0 CASE / 91 WOMEN RANDOMIZED TO ORLISTAT 30 MG TID
1 CASE /579 WOMEN RANDOMIZED TO PLACEBO

3.2.1 CASES IN WOMEN RANDOMIZED TO ORLISTAT 120 MG TID

OF THE NINE WOMEN WITH "ON-STUDY" DIAGNOSES OF BREAST CANCER AFTER RANDOMIZATION TO ORLISTAT 120 MG TID, EIGHT WERE DIAGNOSED WHILE TAKING ORLISTAT 120 MG TID OR WITHIN TWO WEEKS OF STOPPING, AND ONE WAS DIAGNOSED WHILE TAKING ORLISTAT 60 MG TID AFTER HAVING COMPLETED A YEAR OF ORLISTAT 120 MG TID, IN A CROSSOVER TRIAL.

BETWEEN RANDOMIZATION TO ORLISTAT 120 MG TID AND THE DIAGNOSIS OF BREAST CANCER IN THESE NINE WOMEN, THE TIME IN DAYS AND THE WEIGHT CHANGE, IN KILOGRAMS AND AS A PERCENT OF BASELINE, WERE AS FOLLOWS:

	---------WEIGHT CHANGE----------	
TIME (DAYS)	KILOGRAMS	PERCENT OF BASELINE
41	-3.5	
80	+1.4	
178	+2.9	
198	-10.7	
358	-12.6	
436	-3.8	
475	-2.6	
678	-6.4	
709	-0.1	
MEAN= 350	MEAN= -3.9	

THE PROCESS LEADING TO DIAGNOSIS OF BREAST CANCER BEGAN WITH ROUTINE MAMMOGRAPHIES FOR FIVE OF THE NINE WOMEN, WITH A ROUTINE PHYSICAL EXAMINATION FOR ONE, AND WITH BIOPSY OF SYMPTOMATIC BREAST MASSES FOR THREE.

THREE OF THE NINE WOMEN WERE TREATED WITH MASTECTOMY, TWO WITH BREAST SURGERY + RADIOTHERAPY, TWO WITH BREAST SURGERY + RADIOTHERAPY + CHEMOTHERAPY, AND ONE UNKNOWN METHODS. THE ONE WITH A DIAGNOSIS OF CARCINOMA IN SITU WAS TREATED WITH EXCISIONAL BIOPSY.

3.2.2 CASES IN WOMEN RANDOMIZED TO ORLISTAT 60 MG TID

THE ONE WOMAN WITH AN "ON-STUDY" DIAGNOSIS OF BREAST CANCER AFTER RANDOMIZATION TO ORLISTAT 60 MG TID WAS DIAGNOSED ONE DAY AFTER STOPPING ORLISTAT 60 MG TID, AND 37 DAYS AFTER RANDOMIZATION. SHE LOST 3.0 KG BETWEEN RANDOMIZATION AND DIAGNOSIS. THE PROCESS LEADING TO HER DIAGNOSIS BEGAN WITH AN EXAMINATION PRIOR TO ELECTIVE BREAST REDUCTION SURGERY. SHE WAS TREATED WITH MASTECTOMY.

3.2.3 CASES IN WOMEN RANDOMIZED TO PLACEBO

THE ONE WOMAN WITH AN "ON-STUDY" DIAGNOSIS OF BREAST CANCER AFTER RANDOMIZATION TO PLACEBO WAS DIAGNOSED WHILE TAKING PLACEBO, 443 DAYS AFTER RANDOMIZATION. SHE LOST 2.1 KG BETWEEN RANDOMIZATION AND DIAGNOSIS. THE PROCESS LEADING TO HER DIAGNOSIS BEGAN WITH ROUTINE MAMMOGRAPHY. SHE WAS TREATED WITH MASTECTOMY.

3.3 TELEPHONE SURVEY FOR BREAST CANCER DIAGNOSED "OFF STUDY" DURING THE CLINICAL TRIALS AND BREAST CANCER DIAGNOSED AFTER COMPLETION OF THE CLINICAL TRIALS

DURING JULY-OCTOBER 1997, 1454 (89%) OF THE 1642 WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION IN THE SEVEN PHASE 3 CLINICAL OF ORLISTAT WERE INTERVIEWED IN A TELEPHONE SURVEY. THIRTY OF THE 1642 WOMEN (2%) REFUSED TO BE INTERVIEWED, EIGHT (<1%) HAD DIED, AND 150 (9%) COULD NOT BE CONTACTED.

THE INTERVIEW RATE WAS 88% FOR WOMEN IN THE U.S. AND 89% FOR WOMEN IN EUROPE AND THE U.K. INTERVIEW RATES BY TREATMENT GROUP AT THE BEGINNING OF THE TRIALS WERE:

665/747 (89%) RANDOMIZED TO ORLISTAT 120 MG TID
290/316 (89%) RANDOMIZED TO ORLISTAT 30-60 MG TID
509/579 (88%) RANDOMIZED TO PLACEBO

OF THE 1454 WOMEN WHO COMPLETED THE TELEPHONE INTERVIEWS, THREE REPORTED DIAGNOSES OF BREAST CANCER THAT OCCURRED "OFF-STUDY" DURING THE CLINICAL TRIALS OR THAT OCCURRED AFTER COMPLETION OF THE TRIALS:

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 59 YEARS OF AGE, THAT OCCURRED 292 DAYS AFTER RANDOMIZATION TO PLACEBO IN A TWO-YEAR TRIAL. SHE HAD STOPPED PLACEBO 112 DAYS AFTER RANDOMIZATION.

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 55 YEARS OF AGE, THAT OCCURRED 1462 DAYS (4.0 YEARS) AFTER RANDOMIZATION TO ORLISTAT 120 MG TID IN A 2-YEAR TRIAL. SHE HAD COMPLETED THE STUDY.

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 51 YEARS OF AGE, THAT OCCURRED 1520 DAYS (4.2 YEARS) AFTER RANDOMIZATION IN A 2-YEAR CROSSOVER TRIAL TO ORLISTAT 120 MG TID FOR YEAR 1, FOLLOWED BY ORLISTAT 60 MG TID, FOR YEAR 2. SHE HAD COMPLETED THE STUDY.

3.4 FOLLOW-UP TELEPHONE SURVEY FOR THE DISTRIBUTION, AT RANDOMIZATION, OF KNOWN RISK FACTORS FOR BREAST CANCER

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3.5 TABULAR DESCRIPTION OF THE CLINICAL TRIALS AND NARRATIVE SUMMARIES FOR THE WOMEN WITH DIAGNOSES OF BREAST CANCER

TABLE 1 DESCRIBES EACH OF THE SEVEN PHASE 3 CLINICAL TRIALS BY PROTOCOL NUMBER, GEOGRAPHIC LOCATION, BEGINNING AND ENDING YEAR, NUMBER OF WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION, NUMBER OF WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION WHO COMPLETED THE TRIAL, AND THE NUMBER OF WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION WHO RECEIVED DIAGNOSES OF BREAST CANCER.

APPENDIX 1 GIVES CASE REPORTS FOR THE 11 WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION WHO RECEIVED DIAGNOSES OF BREAST CANCER WHILE THEY WERE "ON-STUDY" IN THE CLINICAL TRIALS, AND FOR THE THREE WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION WHO REPORTED IN THE TELEPHONE SURVEY THAT THEY HAD RECEIVED DIAGNOSES OF BREAST CANCER WHILE THEY WERE "OFF-STUDY" DURING THE CLINICAL TRIALS (ONE WOMAN) OR AFTER COMPLETION OF THE TRIALS (TWO WOMEN).

4. ATTACHMENT: STATISTICAL REVIEW BY DR. LEE PIAN, DATED

TABLE 1

PHASE 3 CLINICAL TRIALS OF ORLISTAT
-- WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION --

PROTOCOL/ TREATMENT	RANDOMIZED N	COMPLETED N (%)	BREAST CANCER DIAGNOSIS N/ PATIENT ID NUMBERS
----------ONE YEAR STUDIES----------			
14119B UK,1992-94			
120 MG TID	37	26 (70)	0
PLACEBO	38	24 (63)	0
14302 USA, 1993-96			
120 MG TID	93	70 (75)	2/ JDL68,KTM40
60 MG TID	68	55 (81)	0
30 MG TID	91	74 (81)	0
PLACEBO	90	68 (76)	0
14336 USA, 1993-96			
120 MG TID	73	63 (86)	0
PLACEBO	58	39 (67)	0
----------TWO YEAR STUDIES----------			
14149 EUR, 1993-96			
120 MG TID	98	68 (69)	3/ I007,A065,D010
60 MG TID	95	64 (67)	1/ F006
PLACEBO	108	74 (69)	1/ HO23
14161 USA, 1993-95			
120 MG TID	66	45 (68)	1/ AL18
60 MG TID	62	40 (65)	0
PLACEBO	57	29 (51)	0

Medical Officer Consult

Review: NDA 20-766, Xenical™ (Orlistat)
Sponsor: Hoffmann-La Roche Inc.
HFD-510 Contact: Eric Colman, M.D.

Submission Received (HFD-150): December 18, 1997
Reviewing Medical Officer: Karen Johnson, M.D.
Review completed: January 16, 1998

Background: An NDA for orlistat was submitted November 26, 1996 with presentation at the May 14, 1997 Metabolic and Endocrinologic Advisory Committee meeting. Withdrawal of the NDA was requested in August, 1997. Orlistat is a "potent, selective, and slowly reversible inhibitor of pancreatic lipase", which was developed as a pharmacologic treatment for obesity. The mechanism of action is an approximate 30% decrease in intestinal absorption of ingested fat secondary to reduced conversion of triglycerides to free fatty acids. Safety data for orlistat is based on 4,000 patients, of whom 800 individuals received orlistat for 2 full years. As part of the safety evaluation of orlistat, the numbers of cancers identified during protocol treatment were compared. The distribution of cancers other than breast cancer was similar for orlistat and placebo. In the case of breast cancer, when the study blind was broken for phase 3 studies, there were 11 cases of breast cancer noted, with 10 occurring in orlistat recipients. This submission observes, "The FDA review of the eleven breast cancer cases was briefly addressed in the draft Medical Review of the serious adverse events presented in the Agency's briefing document for the Advisory Committee in preparation for the May 14th meeting. This review (prepared in April of 1997) concludes that orlistat, in all probability, was not a causative agent in these cancers due to lack of biological plausibility...". Subsequently, the sponsor obtained follow-up data on all studies enrolling female patients who were 45 years of age or older. An additional 3 cases of breast cancer were identified. The purpose of this consult is to provide an evaluation of the breast cancer data provided, including an estimate of the potential risk attributable to orlistat.

Reviewer Conclusion: Clinical information related to a possible association between orlistat use and the risk of developing breast cancer is inconclusive.

Specific Comments:

Breast Cancer Case Identification Criteria: If there is suitable evidence that an invasive breast cancer lesion is established prior to the start of a study drug, then such a case should be considered pre-existing and not suitable for an analysis of association. (Examples of suitable evidence: A clinically unevaluated palpable breast mass prior to study entry, a radiologically observed abnormality of the breast judged to require follow-up studies, invasive cancer diagnosed within 6 months of study entry). Using this approach, nine of 14 "cases" are eliminated as suitable for an analysis of association. In addition, 2 more cases are potentially confounded by concurrent use of estrogen replacement therapy with study drug. Questions remain about the other 3 cases as to whether they might contribute information to an analysis of association between orlistat and the development of breast cancer. In the absence of validated orlistat-associated breast cancer cases, there is no way to assess the potential risk of developing breast cancer attributable to orlistat. A review of breast cancer cases from the orlistat database is summarized in the following table.

BREAST CANCER CASES FROM THE ORLISTAT DATABASE

Patient ID	Intervention	Suitable for Analysis	Reason	Other Issues
[redacted]	Orlistat (120 mg)	No	Not cancer, but LCIS	Concurrent Estrogen Replacement Therapy (ERT)
		No	Detection @ 32 days of study drug	
		No	Detection @ 55 days of study drug	
		No	Pre-existing lesion. (Abnormal pre-treatment studies 5 months before randomization)	FNA sampling error. Abnormal studies 4 and 7 months post randomization.
		?	Possible 5mm mass on pre-treatment mammogram. ? suspicious (? calcifications)	Original films needed for blinded review ("Poor quality" copies, central reader knew of subsequent diagnosis)
		No	No pre-study mammogram	
		?	Central review of mammogram alleges a suspicious lesion on pre-treatment films. Photographs insufficient for review	Blinded review of mammograms needed to assess appropriateness of outside decision to watch
		No	No pre-study mammogram	Concurrent ERT
		Possibly Confounded	Concurrent ERT	Incomplete file. No central reading of baseline mammogram
		No	No pre-study mammogram	
	↓	No	No pre-study mammogram	
[redacted]	Orlistat (60 mg)	No	Detection @ 36 days of study drug	
	Placebo	?	0.8 x 0.6 x 0.9 cm mass 0.9 with irregular margins present '87, '89, '91, '92	Blinded review needed to assess if outside reading/management was appropriate
	"	Possibly Confounded	Concurrent ERT	

Breast Cancer Case Imbalance: Although the breast cancer cases in the orlistat trial arms were pre-existing, there should have been a proportional number of pre-existing cases in the placebo arms. The observed imbalance may be due to chance. Additional observation is needed to resolve this concern.

Biologically Plausible Mechanisms for Orlistat-associated Breast Cancer: In the absence of preclinical data reflecting a mutagenic risk related to orlistat, it seems unlikely that a future problem will come to attention from that direction. However, it is possible to speculate that there might be a promotional effect related to orlistat that is not in evidence from current data but could be uncovered by additional studies. If the possibility of a comprehensive epidemiological data collection were pursued, it might be of interest to address the following issues:

1. Relative difference between cases and controls with regard to serum lipids or bile acid profile
2. Differences in hormonal profiles possibly related to an orlistat-induced change in the enterohepatic circulation or hormones
3. Case vs. control differences in levels of fat soluble vitamins
4. A discernible pattern in tumor hormone receptor status

The absence of an effect in ancillary studies might not have been sufficient to detect an effect in patients at risk for breast cancer. Breast cancer cases might have been the exceptions in terms of changes that were not detected in a general subset of the obese population. Before additional work along these lines could be performed, appropriate cases would have to be identified. It does not appear that such cases can be identified from the orlistat data base.

Similar Safety Issues with Other Drugs: There is an accepted association between the use of estrogen-based hormone replacement therapy and breast cancer risk. The Premarin label addresses this issue under Contraindications and Warnings and advises regular breast exams. Compared to estrogen, the evidence for breast cancer risk secondary to orlistat is much less apparent at this time.

Recommendations:

1. Although there is an absence of evidence that could be used to evaluate an association between orlistat and the risk of developing breast cancer, the observed imbalance in breast cancer cases identified in the orlistat safety data base may justify the collection of additional safety data until there is more confidence about the estimate of oncogenic risk, if any, with the use of this drug. A registry should be established for the collection of tumor data in patients who receive orlistat post marketing approval.
2. If approved, product labeling for orlistat should address issues related to breast cancer risk. Language similar to that used in Premarin labeling could be used as a template for orlistat labeling.
3. For any future investigational use, study protocols should specify an appropriate pre-therapy clinical evaluation of breast tissue, so that there is reasonable certainty that patients with untreated breast cancer are not being randomized to a clinical trial.

/S/ [redacted]

Karen Johnson, M.D., Ph.D.

Agree, /S/ [redacted] 1/14/98

cc: Orig. NDA 20-766
HFD-570/Division File
HFD-150/J. Beitz
HFD-150/K. Johnson
HFD-150/D. Pease/consult file
HFD-101/R. Temple
HFD-510/S. Sobel/E. Colman/M. Hess
HFD-102/J. Bilstad

APPEARS THIS WAY ON ORIGINAL